

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
30 November 2000 (30.11.2000)

PCT

(10) International Publication Number  
**WO 00/71122 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/44,**  
A61P 1/04

(21) International Application Number: **PCT/US99/11389**

(22) International Filing Date: **20 May 1999 (20.05.1999)**

(25) Filing Language: **English**

(26) Publication Language: **English**

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(81) Designated States (national): AE, AL, AM, AT, AU, AZ,  
BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,  
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,  
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,  
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,  
SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ,  
VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM,  
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,  
BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,  
NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,  
GN, GW, ML, MR, NE, SN, TD, TG).

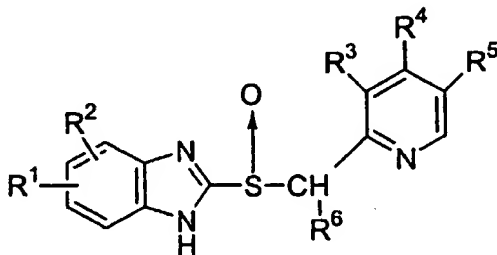
Published:

- With international search report.
- With amended claims.

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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: **STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS**



(I)

(57) Abstract: A novel composition comprising a compound of formula(I) wherein R<sup>1</sup> and R<sup>2</sup> are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl, and ethyl; and R<sup>3</sup> and R<sup>5</sup> are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy

and ethoxyethoxy; and R<sup>4</sup> is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula (II) R<sup>7</sup>CO<sub>2</sub>M where in R<sup>7</sup> is an organic radical and M is a cation, a pharmaceutical formulation containing the composition, methods of preventing or reducing ulceration of the gastrointestinal tract by anti-inflammatory agents using the composition, and methods of stabilizing the composition are described.

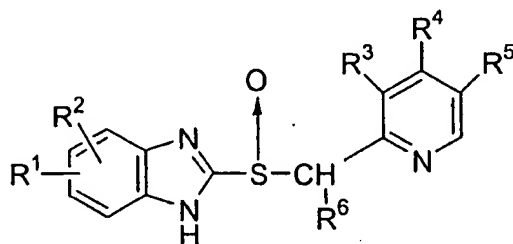
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## STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS

Anti-inflammatory agents, notably agents characterized by the presence of a carboxylic acid group, suffer from a serious side effect, namely, ulceration of the gastrointestinal tract, when administered orally. For example, naproxen, 2-(6-methoxy-2-naphthyl)propionic acid, which is marketed as Naprosyn® in the United States, causes severe ulceration of the stomach and duodenum. Substituted 2-(2-benzimidazolyl)pyridines are known to inhibit gastric acid secretion in mammals, including man. One such compound, 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, omeprazole, which is marketed under the brand name Losec®, is a potent inhibitor of gastric acid secretion and thereby useful for the treatment of peptic ulcer disease. Like the aforementioned anti-inflammatory agents, the 2-(2-benzimidazolyl)pyridines, particularly omeprazole, suffer from a serious defect, namely, instability under physiological conditions. It would thus be desirable to take advantage of the anti-inflammatory properties of the organic carboxylic acids, and at the same time, the gastric acid inhibiting properties of the 2-(2-benzimidazolyl)pyridines, while enhancing the stability of the gastric acid inhibitor. By so doing, a stabilized composition for the treatment of inflammatory disease conditions such as osteoarthritis and rheumatoid arthritis, without the attendant ulceration of the gastrointestinal tract would be available for treatment of inflammation. It has now been found that this goal is achieved when a composition of a 2-(2-benzimidazolyl)pyridines and a salt of an anti-inflammatory organic acid is administered to a patient suffering from inflammatory disease, the salt of the organic

acid ameliorating the inflammation and stabilizing the antiulcerogenic 2-(2-benzimidazolyl)pyridine.

The present invention relates to a composition comprising a compound of



formula I

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wherein R<sup>1</sup> and R<sup>2</sup> are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; and R<sup>3</sup> and R<sup>5</sup> are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R<sup>4</sup> is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II



15 wherein R<sup>7</sup> is an organic radical and M is a cation, useful for the treatment of inflammation with concomitant prevention or reduction of the ulceration of the gastrointestinal tract, and stabilization of the antiulceration compound of formula I. The present invention also relates to a pharmaceutical formulation containing the composition and a method of preparing the formulation.

Subgeneric to the composition are compositions wherein:

- (a)  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is hydrogen; and  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof;
- (b)  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl;  $R^3$  is methyl;  $R^4$  is methoxy; and  $R^5$  is methyl; or a pharmaceutically acceptable acid addition salt thereof;
- (c)  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl;  $R^3$  is hydrogen;  $R^4$  is methoxy; and  $R^5$  is methyl, or  $R^3$  is methyl,  $R^4$  is methoxy and  $R^5$  is hydrogen; or a pharmaceutically acceptable acid addition salt thereof;
- (d)  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl;  $R^3$  and  $R^5$  are selected from the group consisting of hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof;
- (e)  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and

alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl, and R<sup>3</sup> and R<sup>5</sup> are methyl; and R<sup>4</sup> is hydrogen; or a pharmaceutically acceptable acid addition salt thereof;

(f) R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup> and R<sup>5</sup> are hydrogen; and R<sup>4</sup> is ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

(g) R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are methyl; or a pharmaceutically acceptable acid addition salt thereof; and

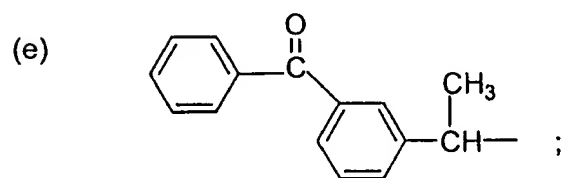
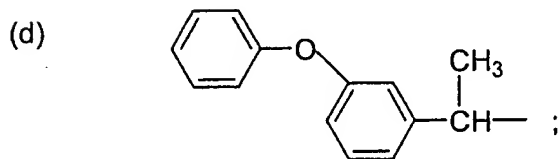
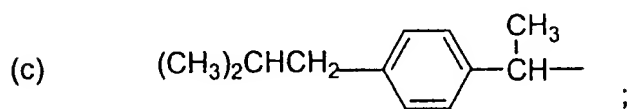
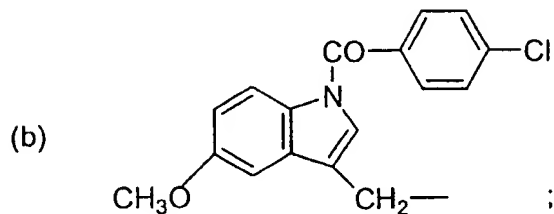
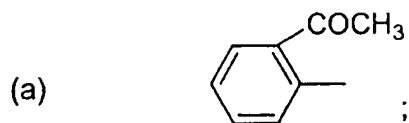
(h) A composition according to claim 1 wherein R<sup>1</sup> is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethoxy; R<sup>2</sup> is hydrogen or methyl; R<sup>6</sup> is hydrogen, methyl or ethyl; R<sup>3</sup> and R<sup>5</sup> are methyl; and R<sup>4</sup> is methoxy, or in which R<sup>1</sup> is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R<sup>2</sup> is hydrogen, methyl or ethyl; R<sup>4</sup> is methoxy; and R<sup>3</sup> is methyl R<sup>5</sup> is hydrogen, or R<sup>3</sup> is hydrogen and R<sup>5</sup> is methyl, or a pharmaceutically acceptable acid addition salt thereof.

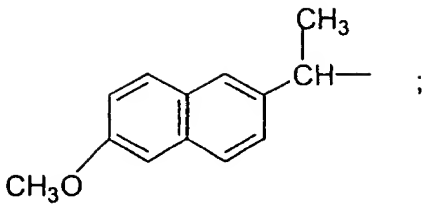
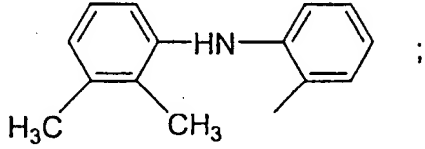
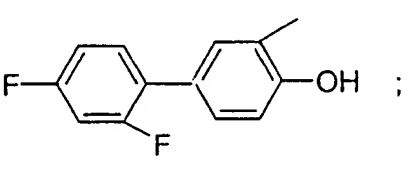
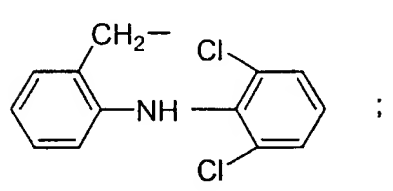
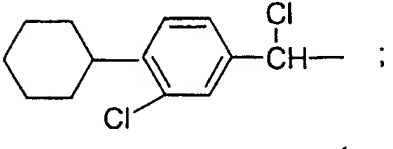
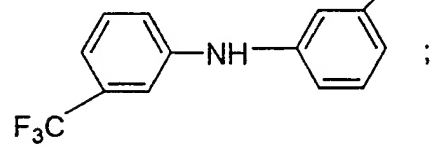
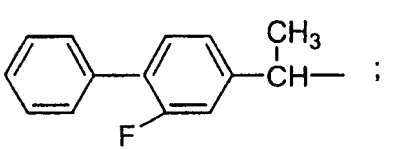
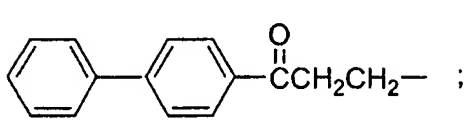
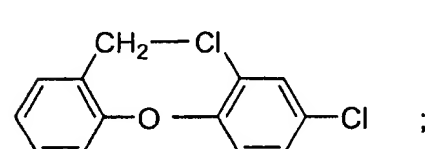
Preferred compositions are those wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)-benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-4,6-dimethyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-

- acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

More preferred is one wherein  $R^1$  is hydrogen;  $R^2$  is methoxy;  $R^3$  and  $R^5$  are methyl;  $R^4$  is methoxy; and  $R^6$  is hydrogen which is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

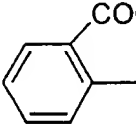
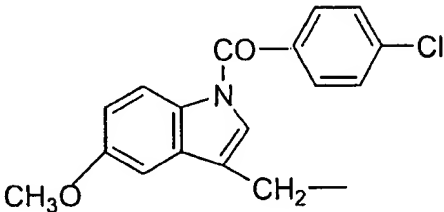
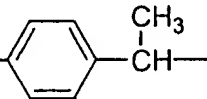
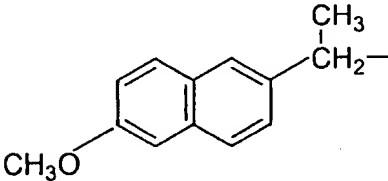
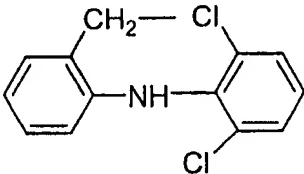
Also subgeneric thereto are compositions where the organic radical is selected from the group consisting of:



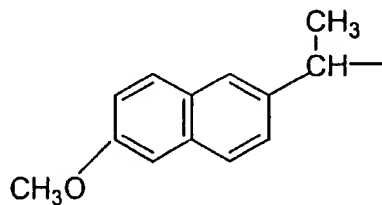
- (f)  ;  
COc1ccccc1C(C)S
- (g)  ;  
Cc1ccccc1NC2=CC=C(C)C=C2
- (h)  ;  
Oc1ccc(cc1)-c2cc(F)c(F)cc2
- (i)  ;  
Clc1ccccc1NC(Cc2ccccc2Cl)N
- (j)  ;  
Clc1ccccc1NC(Cc2ccccc2Cl)N
- (k)  ;  
C(F)(F)Fc1ccccc1NC2=CC=CC=C2
- (l)  ;  
Cc1ccccc1NC(C)Nc2ccccc2F
- (m)  ;  
CC(=O)Nc1ccc(cc1)-c2ccccc2
- (n)  ;  
Clc1ccccc1NC(Cc2ccccc2Cl)N



Compositions wherein the organic radical is selected from the group consisting of:

- (o)  ;
- (p)  ;
- (q)  $(\text{CH}_3)_2\text{CHCH}_2$   ;
- (r)  ; and
- (s)  are more preferred.

A most preferred composition is one wherein the organic radical is

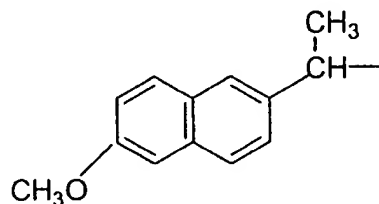


(a) a composition wherein M is sodium, potassium, magnesium, calcium, or aluminum; and

(b) a composition wherein M is sodium.

A most preferred composition is one wherein R<sup>1</sup> is hydrogen; R<sup>2</sup> is methoxy;

5 R<sup>3</sup> and R<sup>5</sup> are methyl; R<sup>4</sup> is methoxy; R<sup>6</sup> is hydrogen; R<sup>7</sup> is



and M is sodium.

As used through the specification and appended claims, the term “alkyl” refers to a straight or branched chain hydrocarbon radical containing no unsaturation and having 1 to 10 carbon atoms. Examples of alkyl groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-pentyl, 3-hexyl, 4-heptyl, 2-octyl, 3-nonyl, 4-decyl and the like.

10 The term “alkanol” refers to a compound formed by a combination of an alkyl group and hydroxy radical. Examples of alkanols are methanol, ethanol, 1- and 2-propanol, 2,2-dimethylethanol, hexanol, octanol, decanol and the like. The term “alkanoic acid” refers to a compound formed by combination of a carboxyl group with a hydrogen

15 atom or alkyl group. Examples of alkanoic acids are formic acid, acetic acid, propanoic acid, 2,2-dimethylacetic acid, hexanoic acid, octanoic acid, decanoic acid and the like. The term “halogen” refers to a member of the family fluorine, chlorine, bromine, or iodine. The term “alkanoyl” refers to the radical formed by removal of the hydroxyl function from an alkanoic acid. Examples of alkanoyl groups are

20 formyl, acetyl, propionyl, 2,2-dimethylacetyl, hexanoyl, octanoyl, decanoyl and the

like. The term "lower" as applied to any of the aforementioned groups refers to a group having a carbon skeleton containing up to an including 8 carbon atoms.

The compounds of the present invention which lack an element of symmetry exist as optical antipodes may be prepared from the corresponding racemic forms by  
5 standard optical resolution techniques, involving, for example, the separation of diastereomeric salts of those instant compounds characterized by the presence of a carboxylic acid group and an optically active base, or by synthesis from optically active precursors.

The present invention comprehends all optical isomers and racemic forms  
10 thereof and all geometric isomers of the compounds disclosed and claimed herein. The formulas of the compounds shown herein are intended to encompass all possible geometric and optical isomers of the compounds so depicted.

The 2-(2-benzimidazolyl)pyridines and the methods of preparation thereof are described in U.S. Patent 4,255,431 granted March 10, 1981 to U.K. Junggren and S.E.  
15 Sjöstrand, as is their antisecretory inhibitory properties.

The organic carboxylic acids and their anti-inflammatory properties, as well as their ulcerogenic effects are described in U.K. Patent Application GB 2 105 193 A.

The salts of the organic carboxylic acids are known or are prepared by conventional methods, for example, treatment of a carboxylic acid with an alkali  
20 metal or alkaline earth metal in a suitable solvent such as alkanol, e.g., methanol, ethanol, 2-propanol, and the like, and aqueous combinations thereof.

The stabilization of a 2-(2-benzimidazolyl)pyridine by a salt of an organic carboxylic acid in an aqueous medium is demonstrated in a conventional assay. In the

assay, the 2-(2-benzimidazolyl)pyridine is dissolved in water and the stability thereof is determined and compared to that of a solution of a 2-(2-benzimidazolyl)pyridine and a salt of an organic acid in water.

In a specific assay, omeprazole (10 mg) is dissolved in water (100 ml) at room temperature, and samples are removed periodically and assayed for omeprazole by high performance liquid chromatography on a column of Hypersil (250 x 4.6 mm ) using 0.02 M ammonium acetate buffer: acetonitrile (65:35). The presence of omeprazole is detected by ultraviolet spectroscopy at a wavelength of 235 nm.

The results are shown in the table:

Time, hr	Omeprazole in water, %	Omeprazole+Naproxen Na in water, %
0	100	100
2	95.8	97.7
19	69.8	94.9

10

Effective quantities of the compositions of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

The active compositions of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral

20

therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, suppositories, chewing gum and the like. These preparations should contain at least 0.5% of active compositions, but may be varied  
5 depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 milligrams of active compound.

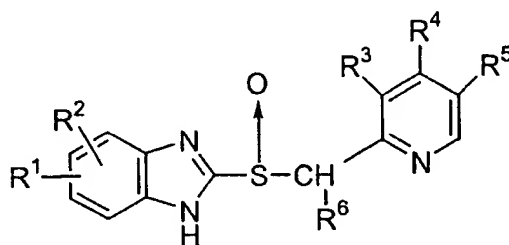
10 The tablets, pills, capsules, troches, suppositories and the like may also contain the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening  
15 agent and certain preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active composition of the invention may be incorporated into a solution or suspension.  
20 These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present inventions are

prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound.

The solutions or suspensions may also include the following components: a steril diluent such as water for injection, saline solution, fixed oils, polyethylene  
 5 glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in disposable syringes or multiple dose vials  
 10 made of glass or plastic.

Included among pharmaceutical formulations are stabilized pharmaceutical unit dosage forms comprising a core (a) comprising a compound of formula I



15

wherein R<sup>1</sup> and R<sup>2</sup> are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl, and R<sup>3</sup> and R<sup>5</sup> are the same or different and are each selected from the group consisting of

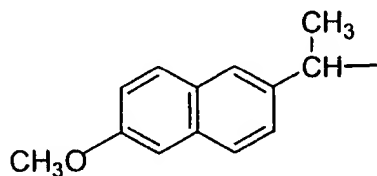
hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and  $R^4$  is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II



wherein  $R^7$  is an organic radical and M is a cation;

- (b) a first coating of the core comprising at least one layer of a polymeric coating; and
- (c) a second coating comprising an enteric coating.

Preferred stabilized pharmaceutical unit dosage forms are those wherein the compound of formula I comprises compounds wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carbethoxy, alkoxy and alkanoyl;  $R^6$  is hydrogen; and  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy; and ethoxy; or a pharmaceutically acceptable acid addition salt thereof and the compound of formula II wherein the organic radical is selected from the group consisting of



wherein M is sodium, potassium, calcium, barium or aluminum.

More preferred stabilized pharmaceutical unit dosage forms are those wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-

(5-methoxy)benzimidazole and the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

The stabilized pharmaceutical dosage forms of the present invention are formulated by granulating a mixture of the compounds of formulas I and II.

- 5 Pharmaceutically acceptable excipients, for example, fillers, binders and lubricants may be included in the granulation for the purpose of facilitating the granulation and improving the acceptance of the ultimate tablet. Among fillers there may be mentioned hydroxyalkylcellulose, particularly hydroxypropylcellulose. Among binders there may be mentioned polyvinylpyrrolidone. Among lubricants there may be
- 10 mentioned talc and magnesium.

- The granulate is first coated with at least one layer of a polymeric coating, for example a hydroxyalkylalkylcellulose, polyethylene glycol and a pigment coating, particularly a coating containing hydroxypropylmethylcellulose. The coated granulate is then coated with an enteric coating comprising a methacrylic acid
- 15 copolymer. Among methacrylic acid copolymers there may be mentioned methacrylic acid ethyl acrylate copolymer.

- The granulation is carried out in conventional equipment using a solvent such as 2-propanol, and the granulate is dried prior to the next operation, i.e., coating the granulate. The first coating is applied by granulating the dried granulate with, for
- 20 example, hydroxypropylmethylcellulose, polyethylene, pigment, preferably in aqueous suspension, also in conventional equipment, followed by drying, i.e., removing the solvent by evaporation under conventional conditions. The dried coated granulate is then coated with a methacrylic acid copolymer, particularly methacrylic



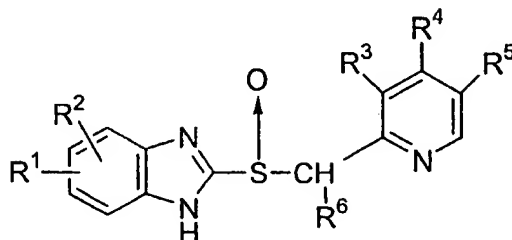
acid ethyl acrylate copolymer to yield the stabilized pharmaceutical dosage form in pellet form.

The granulation and coating steps are generally performed under conventional conditions. In one such granulation and coating procedure, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole (omeprazole) (20 mg/tablet), sodium 2-(6-methoxy-2-naphthyl) propionic acid (naproxen sodium) (550 mg/tablet), hydroxypropylcellulose (30 mg), polyvinylpyrrolidone (30 mg/tablet), talc (5.0 mg/tablet), and magnesium stearate (5.0 mg/tablet) is granulated in 2-propanol, dried, and the dried granulate is first coated with hydroxypropylmethylcellulose, polyethylene glycol, pigment (9mg/tablet), the coated granulate dried and granulated with a methacrylic acid ethyl acrylate copolymer in aqueous suspension and dried to form the tablet.

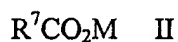
The tablets are stable in the solid form over a reasonably long period of time, showing no significant change in the omeprazole titer. At a temperature of 40°C and relative humidity of 75%, enteric coated tablets of omeprazole and naproxen sodium, prepared as described above, are stable over a period of three months. After three months, the omeprazole titer was determined to be 96.9%, relative to the initial amount, by high performance liquid chromatography.

What is claimed is:

1. A composition comprising a compound of formula I



- wherein  $R^1$  and  $R^2$  are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl, and  $R^3$  and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and  $R^4$  is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II



wherein  $R^7$  is an organic radical and M is a cation.

2. A composition according to claim 1 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy, and alkanoyl,  $R^6$  is hydrogen; and  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof.

3. A composition according to claim 1 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl;  $R^3$  is methyl;  $R^4$  is methoxy; and  $R^5$  is methyl; or a pharmaceutically acceptable acid addition salt thereof.

4. A composition according to claim 1 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl; and  $R^3$  is hydrogen;  $R^4$  is methoxy; and  $R^5$  is methyl or  $R^3$  is methyl,  $R^4$  is methoxy and  $R^5$  is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

5. A composition according to claim 1 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl, and ethyl,  $R^3$  and  $R^5$  are hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof.

6. A composition according to claim 1 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl,  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl; and  $R^3$  and  $R^5$  are methyl; and  $R^4$  is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

7. A composition according to claim 1 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl,

halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup> and R<sup>5</sup> are hydrogen; and R<sup>4</sup> is ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

5                    8.        A composition according to claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl, R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are methyl; or a pharmaceutically acceptable acid addition salt thereof.

10                   9.        A composition according to claim 1 wherein R<sup>1</sup> is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carbethoxy or carbomethoxy; R<sup>2</sup> is hydrogen or methyl; R<sup>6</sup> is hydrogen, methyl or ethyl; R<sup>3</sup> and R<sup>5</sup> are methyl; and R<sup>4</sup> is methoxy, or in which R<sup>1</sup> is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R<sup>2</sup> is hydrogen, methyl or ethyl; R<sup>4</sup> is methoxy; and R<sup>3</sup> is methyl and  
15        R<sup>5</sup> is hydrogen or R<sup>3</sup> is hydrogen and R<sup>5</sup> is methyl, or a pharmaceutically acceptable acid addition salt thereof.

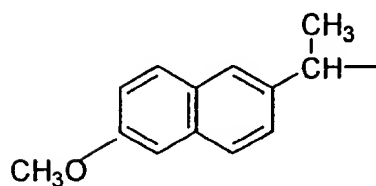
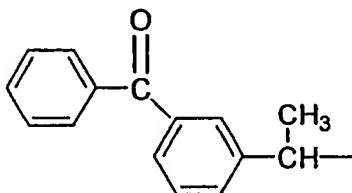
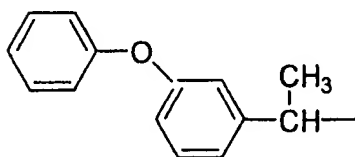
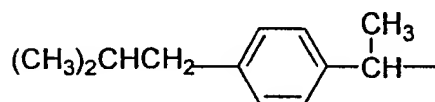
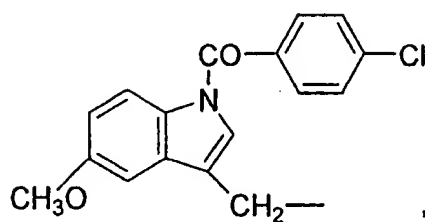
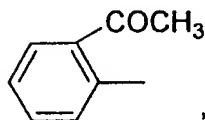
                    10.        A composition according to claim 1 wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-4,6-dimethyl)-benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl-6-methyl)-benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole, 2-[2-

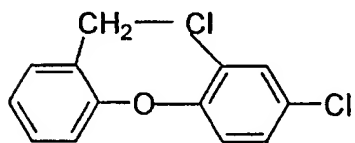
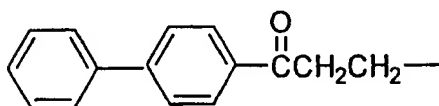
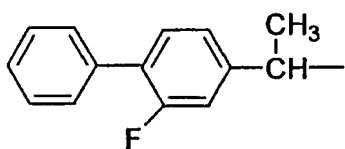
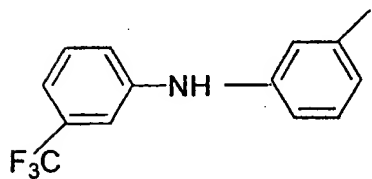
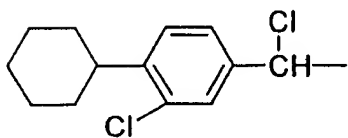
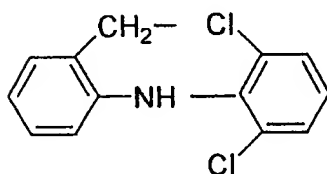
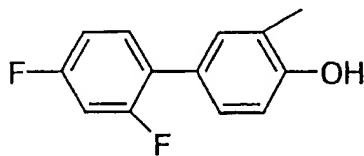
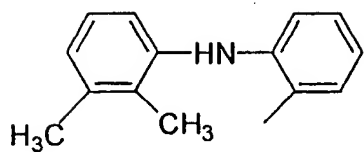
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(3-methyl-4-methoxy)pyridinylmethanesulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethanesulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethanesulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethanesulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

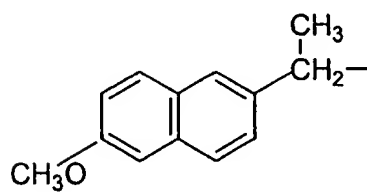
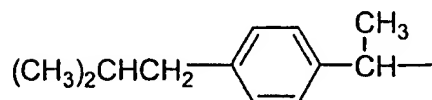
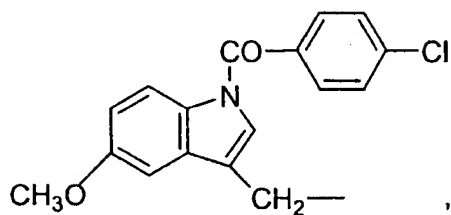
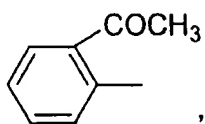
11. A composition according to claim 10 wherein R<sup>1</sup> is hydrogen; R<sup>2</sup> is methoxy; R<sup>3</sup> and R<sup>5</sup> are methyl; R<sup>4</sup> is methoxy; and R<sup>6</sup> is hydrogen which is 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

12. A composition according to claim 1 wherein the organic radical is selected from the group consisting of:

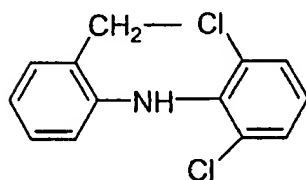




13. A composition according to claim 12 wherein the organic radical is selected from the group consisting of:

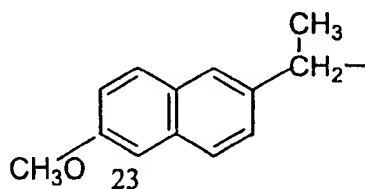


and



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14. The composition according to claim 13 wherein the organic radical is



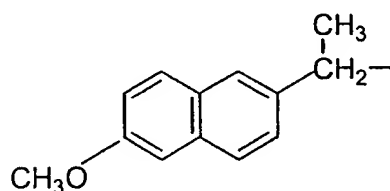


15. A compound according to claim 1 wherein M is sodium, potassium, magnesium, calcium, barium or aluminum.

16. A composition according to claim 15 wherein M is sodium, potassium, calcium, barium or aluminum.

5 17. A composition according to claim 16 wherein M is sodium.

18. A composition according to claim 17 wherein R<sup>1</sup> is hydrogen, R<sup>2</sup> is methoxy; R<sup>3</sup> and R<sup>5</sup> are methyl; R<sup>4</sup> is methoxy; R<sup>6</sup> is hydrogen; R<sup>7</sup> is



and M is sodium.

19. A method of preventing ulceration of the gastrointestinal tract  
10 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 1.

20. A method of preventing ulceration of the gastrointestinal tract  
15 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 2.

21. A method of preventing ulceration of the gastrointestinal tract  
20 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the

gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 3.

22. A method of preventing ulceration of the gastrointestinal tract  
5 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 4.

23. A method of preventing ulceration of the gastrointestinal tract  
10 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 5.

24. A method of preventing ulceration of the gastrointestinal tract  
15 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 6.

25. A method of preventing ulceration of the gastrointestinal tract  
20 by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 7.

26. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing  
5 effective amount of a composition of claim 8.

27. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing  
10 effective amount of a composition of claim 9.

28. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing  
15 effective amount of a composition of claim 10.

29. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing  
20 effective amount of a composition of claim 11.

30. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 12.

31. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 13.

32. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 14.

33. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 15.

34. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 16.

35. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing  
5 effective amount of a composition of claim 17.

36. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing  
10 effective amount of a composition of claim 18.

37. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing  
15 effective amount of a composition of claim 1.

38. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing  
20 effective amount of a composition of claim 2.

39. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 3.

40. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 4.

41. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 5.

42. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 6.

43. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 7.

44. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing  
5 effective amount of a composition of claim 8.

45. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing  
10 effective amount of a composition of claim 9.

46. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing  
15 effective amount of a composition of claim 10.

47. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing  
20 effective amount of a composition of claim 11.

48. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 12.

49. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 13.

50. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 14.

51. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 15.

52. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 16.



53. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 17.

54. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 18.

55. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 1 and a pharmaceutically acceptable carrier therefor.

56. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 2 and a pharmaceutically acceptable carrier therefor.

57. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 3 and a pharmaceutically acceptable carrier therefor.

58. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 4 and a pharmaceutically acceptable carrier therefor.
- 5 59. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 5 and a pharmaceutically acceptable carrier therefor.
- 10 60. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 6 and a pharmaceutically acceptable carrier therefor.
- 15 61. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 7 and a pharmaceutically acceptable carrier therefor.
- 20 62. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 8 and a pharmaceutically acceptable carrier therefor.
63. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 9 and a pharmaceutically acceptable carrier therefor.

64. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the  
5 active ingredient a composition of claim 10 and a pharmaceutically acceptable carrier therefor.

65. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract in a mammal by an anti-inflammatory agent, comprising as the active ingredient a composition of claim 11 and a pharmaceutically acceptable carrier  
10 therefor.

66. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 12 and a pharmaceutically acceptable carrier therefor.

15 67. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 13 and a pharmaceutically acceptable carrier therefor.

20 68. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 14 and a pharmaceutically acceptable carrier therefor.

69. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 15 and a pharmaceutically acceptable carrier therefor.

5 70. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 16 and a pharmaceutically acceptable carrier therefor.

10 71. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 17 and a pharmaceutically acceptable carrier therefor.

15 72. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 18 and a pharmaceutically acceptable carrier therefor.

20 73. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 1 and a pharmaceutically acceptable carrier therefor.

74. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 2 and a pharmaceutically acceptable carrier therefor.

75. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the  
5 active ingredient a composition of claim 3 and a pharmaceutically acceptable carrier therefor.

76. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 4 and a pharmaceutically acceptable carrier  
10 therefor.

77. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 5 and a pharmaceutically acceptable carrier therefor.

15 78. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 6 and a pharmaceutically acceptable carrier therefor.

79. A pharmaceutical formulation for reducing ulceration of the  
20 gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 7 and a pharmaceutically acceptable carrier therefor.

80. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 8 and a pharmaceutically acceptable carrier therefor.

5 81. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 9 and a pharmaceutically acceptable carrier therefor.

10 82. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 10 and a pharmaceutically acceptable carrier therefor.

15 83. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 11 and a pharmaceutically acceptable carrier therefor.

20 84. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 12 and a pharmaceutically acceptable carrier therefor.

85. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 13 and a pharmaceutically acceptable carrier therefor.

86. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the  
5 active ingredient a composition of claim 14 and a pharmaceutically acceptable carrier therefor.

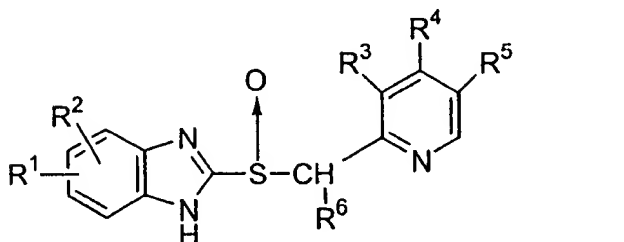
87. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 15 and a pharmaceutically acceptable carrier  
10 therefor.

88. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 16 and a pharmaceutically acceptable carrier therefor.

15 89. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 17 and a pharmaceutically acceptable carrier therefor.

90. A pharmaceutical formulation for reducing ulceration of the  
20 gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 18 and a pharmaceutically acceptable carrier therefor.

91. A method of stabilizing a compound of formula I



wherein  $R^1$  and  $R^2$  are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl; and  $R^3$  and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and  $R^4$  is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof by combining the compound of formula I with a compound of formula II

10  $R^7CO_2M$  II

wherein  $R^7$  is an organic radical and  $M$  is a cation to form a stabilized composition.

92. A method according to claim 91 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy, and alkanoyl,  $R^6$  is hydrogen; and  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof.

93. A method according to claim 91 wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the



group consisting of hydrogen, methyl and ethyl; R<sup>3</sup> is methyl; R<sup>4</sup> is methoxy; and R<sup>5</sup> is methyl; or a pharmaceutically acceptable acid addition salt thereof.

94. A method according to claim 91 wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; and R<sup>3</sup> is hydrogen, R<sup>4</sup> is methoxy; and R<sup>5</sup> is methyl, or R<sup>3</sup> is methyl; R<sup>4</sup> is methoxy and R<sup>5</sup> is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

95. A method according to claim 91 wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup> and R<sup>5</sup> are hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof.

96. A method according to claim 91 wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; and R<sup>3</sup> and R<sup>5</sup> are methyl and R<sup>4</sup> is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

97. A method according to claim 91 wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup> and R<sup>5</sup> are hydrogen; and R<sup>4</sup> is

ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

98. A method according to claim 91 wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl; R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are all methyl; or a pharmaceutically acceptable acid addition salt thereof.

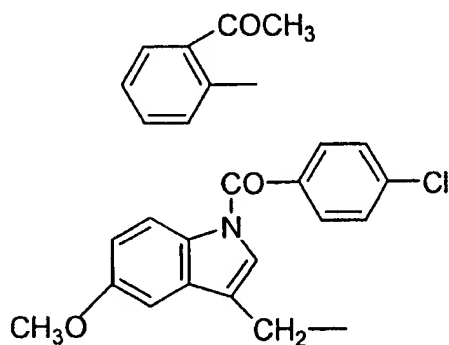
99. A method according to claim 91 wherein R<sup>1</sup> is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethoxy; R<sup>2</sup> is hydrogen or methyl; R<sup>6</sup> is hydrogen, methyl or ethyl; R<sup>3</sup> and R<sup>5</sup> are methyl; and R<sup>4</sup> is methoxy, or in which R<sup>1</sup> is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R<sup>2</sup> is hydrogen, methyl or ethyl; R<sup>4</sup> is methoxy; and R<sup>3</sup> is methyl and R<sup>5</sup> is hydrogen or R<sup>3</sup> is hydrogen and R<sup>5</sup> is methoxy, or a pharmaceutically acceptable acid addition salt thereof.

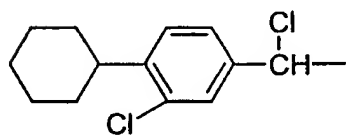
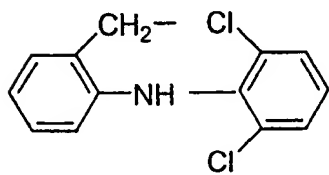
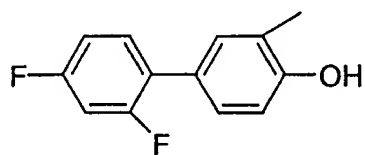
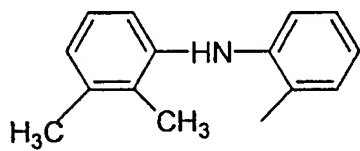
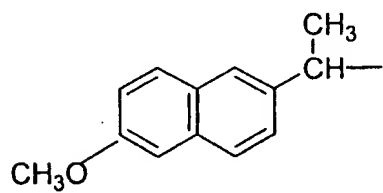
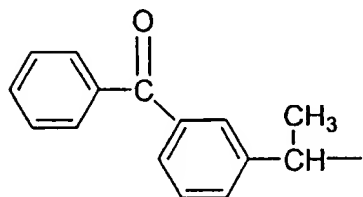
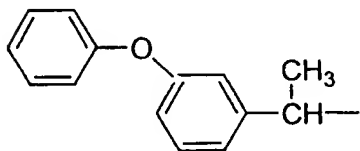
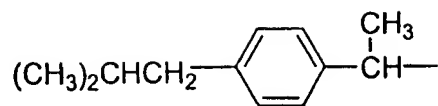
100. A method according to claim 1 wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridylmethysulfinyl]-4,6-dimethyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-

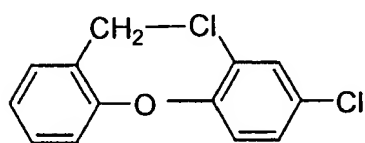
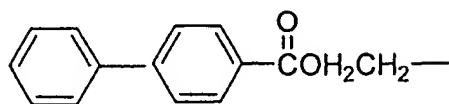
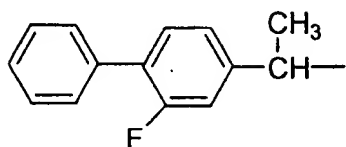
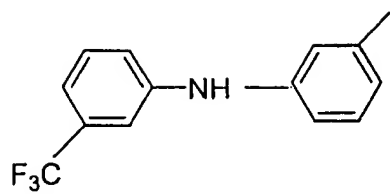
carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

101. A method according to claim 100 wherein  $R^1$  is hydrogen,  $R^2$  is methoxy,  $R^3$  and  $R^5$  are methyl,  $R^4$  is methoxy; and  $R^6$  is hydrogen, which is 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

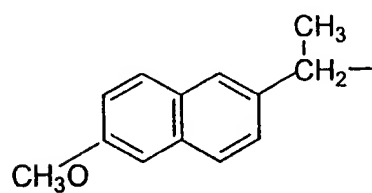
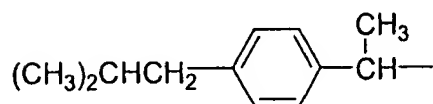
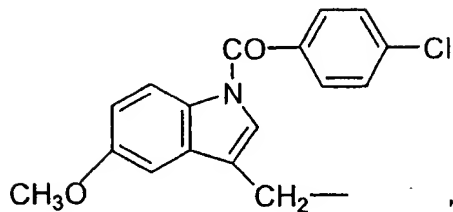
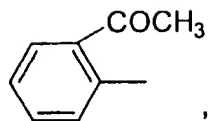
102. A method according to claim 1 wherein the organic radical selected from the group consisting of:



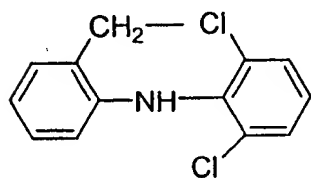




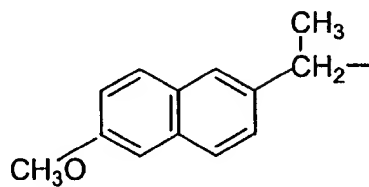
103. A method according to claim 102 wherein the organic radical is selected from the group consisting of:



and



104. A method according to claim 103 wherein the organic radical is

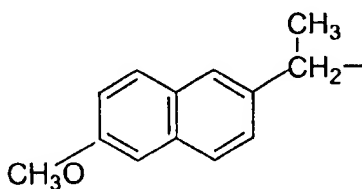


105. The method according to claim 91 wherein M is sodium, potassium, magnesium, calcium, barium or aluminum.

106. The method according to claim 105 wherein M is sodium, potassium, calcium, barium or aluminum.

5 107. The method according to claim 106 wherein M is sodium.

108. The method according to claim 91 wherein R<sup>1</sup> is hydrogen, R<sup>2</sup> is methoxy; R<sup>3</sup> and R<sup>5</sup> are methyl; R<sup>4</sup> is methoxy, R<sup>6</sup> is hydrogen; R<sup>7</sup> is



and M is sodium.

109. A method according to claim 91 wherein the compound to be  
10 stabilized of formula I is in the solid state.

110. A method according to claim 109 wherein the compound to be stabilized is in the fluid state.

111. A method according to claim 110 wherein the compound to be stabilized is in the liquid state.

15 112. A method according to claim 111 wherein the liquid state is a fluid state.

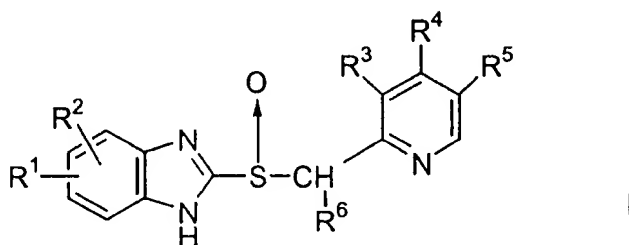
113. A method according to claim 112 wherein the fluid state is an aqueous medium.

114. A method according to claim 113 wherein the aqueous medium is the  
20 medium of the gastrointestinal tract of a mammal.

115. A method according to claim 114 wherein the aqueous medium of the gastrointestinal tract is the medium of the stomach.

116. A method according to claim 115 wherein the aqueous medium of the gastrointestinal tract is the medium of the gut.

5 117. A stabilized pharmaceutical unit dosage form comprising (a) a core comprising a compound of formula I



wherein  $R^1$  and  $R^2$  are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl;  $R^6$  is selected from the group consisting of hydrogen, methyl and ethyl, and  $R^3$  and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and  $R^4$  is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and

15 a compound of formula II



wherein  $R^7$  is an organic radical and M is a cation;

(b) a first coating of the core comprising at least one layer of a polymer coating; and

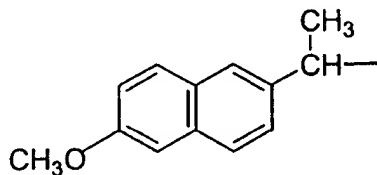
(c) a second coating comprising an enteric coating.



118. A stabilized pharmaceutical unit dosage form comprising a core according to claim 117 wherein the compound of formula I comprises compounds wherein  $R^1$  and  $R^2$  are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carbethoxy, alkoxy and alkanoyl;  $R^6$  is  
5 hydrogen; and  $R^3$ ,  $R^4$ , and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy; and ethoxy; or a pharmaceutically acceptable acid addition salt thereof.

119. A stabilized pharmaceutical unit dosage form according to claim 118 wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)-  
10 pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole.

120. A stabilized pharmaceutical unit dosage form according to claim 117 wherein the organic radical of the compound of formula II is selected from the group consisting of



15 wherein M is sodium, potassium, calcium, barium or aluminum.

121. The stabilized pharmaceutical unit dosage form according to claim 120 wherein the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

122. A stabilized pharmaceutical unit dosage form according to claim 117  
20 wherein the core comprises pharmaceutically acceptable excipients.

123. A stabilized pharmaceutical unit dosage form according to claim 122 wherein excipients comprise a filler, a binder or a lubricant.

124. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the filler is a hydroxyalkylcellulose.

5 125. A stabilized pharmaceutical unit dosage form according to claim 124, wherein the hydroxyalkylcellulose is hydroxypropylcellulose.

126. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the filler is a polyvinylpyrrolidone.

10 127. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the lubricants are talc or magnesium stearate.

128. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the polymer coating comprises a hydroxyalkylcellulose, polyethylene glycol and a pigment.

15 129. A stabilized pharmaceutical unit dosage form according to claim 128, wherein the hydroxyalkylcellulose is hydroxypropylmethylcellulose.

130. A stabilized pharmaceutical unit dosage form according to claim 117, wherein the enteric coating is a methacrylic acid copolymer.

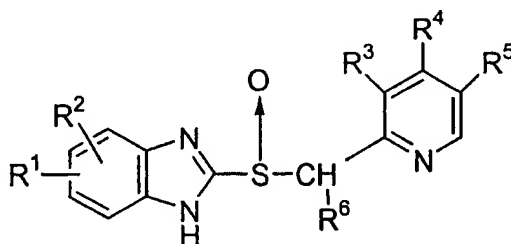
20 131. A stabilized pharmaceutical unit dosage form according to claim 130, wherein the methacrylic acid copolymer is a copolymer of methacrylic acid and ethyl acrylate.

132. A stabilized pharmaceutical unit dosage form according to claim 117, wherein the dosage form is a tablet.

133. A stabilized pharmaceutical unit dosage form according to claim 117, comprising 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxybenzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellulose, polyvinylpyrrolidone, talce and magnesium stearate first  
 5 coated with hydroxypropylmethylcellulose, polyethylent glycol, pigment) and enteric coated with methacrylic acid ethyl acrylate copolymer.

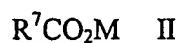
134. A process for the preparation of a stabilized pharmaceutical unit dosage form comprising the steps of:

(a) granulating a mixture of a compound of formula I



10

wherein R<sup>1</sup> and R<sup>2</sup> are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R<sup>6</sup> is selected from the group consisting of hydrogen, methyl and ethyl, and R<sup>3</sup> and R<sup>5</sup> are the same or different and are each selected from the group consisting of  
 15 hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R<sup>4</sup> is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, a compound of formula II



wherein  $R^7$  is an organic radical and M is a cation, a filler, a binder and a lubricant;

- (b) drying the granulation of step (a)
- (c) coating the dried granulation of step (b) with a first coating;
- (d) drying the first coated granulation of step (c);
- 5 (e) coating the dried granulation of step (d) with an enteric coating.

135. The process for the preparation of a stabilized pharmaceutical unit dosage form according to claim 133 comprising the steps of:

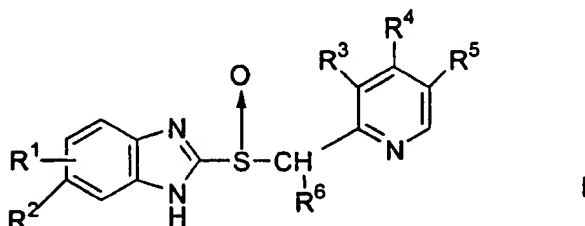
- (a) granulating a mixture of 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole, sodium 2-(6-methoxy-  
10 2-naphthyl)propionic acid, hydroxypropylcellulose, polyvinylpyrrolidone, talc and magnesium stearate;
- (b) drying the granulate in step (a);
- (c) coating the dried granulate of step (b) with a first coating comprising hydroxypropylmethylcellulose, polyethylene glycol and a pigment;
- 15 (d) drying the coated formulate from step (c); and
- (e) coating the dried granulate from step (d) with an enteric coating comprising a methacrylic acid ethyl acrylate copolymer.

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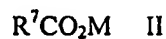
## AMENDED CLAIMS

[received by the International Bureau 04 July 2000 (04.07.00);  
original claims 1-134 replaced by new claims 135- 166 (7 pages)]

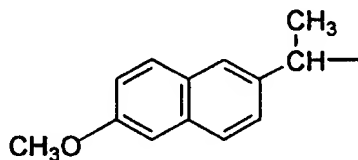
135. A composition comprising a compound of formula I



wherein  $R^1$  hydrogen;  $R^2$  is methoxy;  $R^6$  is hydrogen;  $R^3$  and  $R^5$  are methyl; and  $R^4$  is methoxy or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

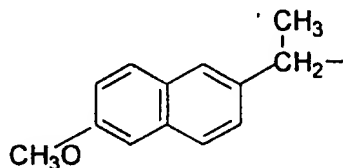


wherein  $R^7$  is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum.

136. A composition according to claim 135 wherein  $R^1$  hydrogen;  $R^2$  is methoxy;  $R^3$  and  $R^5$  are methyl; and  $R^4$  is methoxy,  $R^6$  is hydrogen; and  $R^7$  is a group of the formula



and M is sodium.

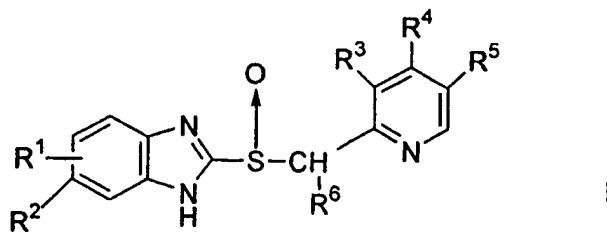
137. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 135.

138. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 136.

139. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 135 and a pharmaceutically acceptable carrier therefor.

140. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 136 and a pharmaceutically acceptable carrier therefor.

141. A method of stabilizing a compound of formula I

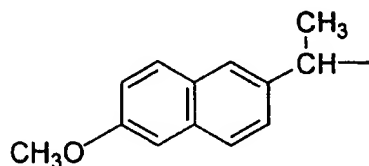


wherein R<sup>1</sup> hydrogen; R<sup>2</sup> is methoxy; R<sup>6</sup> is hydrogen; R<sup>3</sup> and R<sup>5</sup> are methyl; and R<sup>4</sup> is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

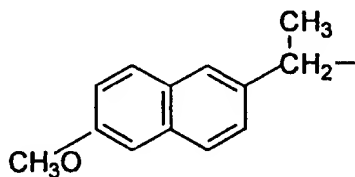


wherein  $R^7$  is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum.

142. The method according to claim 141 wherein  $R^1$  is hydrogen,  $R^2$  is methoxy;  $R^3$  and  $R^5$  are methyl;  $R^4$  is methoxy,  $R^6$  is hydrogen;  $R^7$  is



and M is sodium.

143. A method according to claim 141 wherein the compound of formula I to be stabilized is in the solid state.

144. A method according to claim 141 wherein the compound of formula I to be stabilized is in the fluid state.

145. A method according to claim 144 wherein the compound of formula I to be stabilized is in the liquid state.

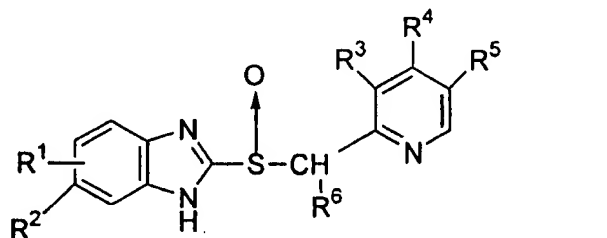
146. A method according to claim 144 wherein the fluid state is an aqueous medium.

147. A method according to claim 146 wherein the aqueous medium is the medium of the gastrointestinal tract of a mammal.

148. A method according to claim 147 wherein the aqueous medium of the gastrointestinal tract is the medium of the stomach.

149. A method according to claim 147 wherein the aqueous medium of the gastrointestinal tract is the medium of the gut.

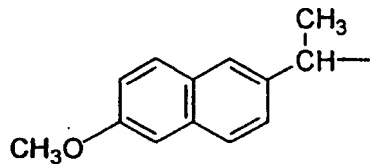
150. A stabilized pharmaceutical unit dosage form comprising (a) a core comprising a compound of formula I



wherein  $R^1$  is hydrogen;  $R^2$  is methoxy;  $R^6$  is hydrogen;  $R^3$  and  $R^5$  are methyl; and  $R^4$  is methoxy or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II



wherein  $R^7$  is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium, potassium, magnesium, calcium, barium and aluminum;



- (b) a first coating of the core comprising at least one layer of a polymer coating; and
- (c) a second coating comprising an enteric coating.

151. A stabilized pharmaceutical unit dosage form according to claim 150 wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole.

152. The stabilized pharmaceutical unit dosage form according to claim 150 wherein the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

153. A stabilized pharmaceutical unit dosage form according to claim 150 wherein the core comprises pharmaceutically acceptable excipients.

154. A stabilized pharmaceutical unit dosage form according to claim 150 wherein excipients comprise a filler, a binder or a lubricant.

155. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the filler is a hydroxyalkylcellulose.

156. A stabilized pharmaceutical unit dosage form according to claim 155, wherein the hydroxyalkylcellulose is hydroxypropylcellulose.

157. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the filler is a polyvinylpyrrolidone.

158. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the lubricants are talc or magnesium stearate.

159. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the polymer coating comprises a hydroxyalkylcellulose, polyethylene glycol and a pigment.

160. A stabilized pharmaceutical unit dosage form according to claim 159, wherein the hydroxyalkylcellulose is hydroxypropylmethylcellulose.

161. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the enteric coating is a methacrylic acid copolymer.

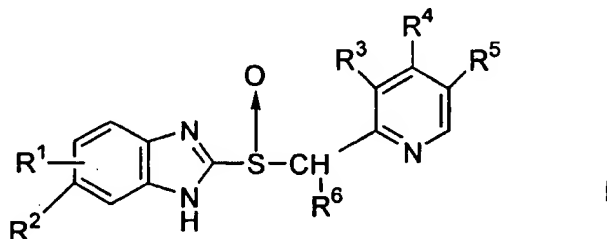
162. A stabilized pharmaceutical unit dosage form according to claim 161, wherein the methacrylic acid copolymer is a copolymer of methacrylic acid and ethyl acrylate.

163. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the dosage form is a tablet.

164. A stabilized pharmaceutical unit dosage form according to claim 150, comprising 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxybenzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellulose, polyvinylpyrrolidone, talc and magnesium stearate first coated with hydroxypropylmethylcellulose, polyethylent glycol, pigment and enteric coated with methacrylic acid ethyl acrylate copolymer.

165. A process for the preparation of a stabilized pharmaceutical unit dosage form comprising the steps of:

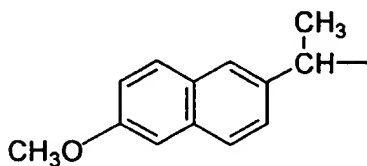
(a) granulating a mixture of a compound of formula I



wherein R<sup>1</sup> hydrogen; R<sup>2</sup> is methoxy; R<sup>6</sup> is hydrogen; R<sup>3</sup> and R<sup>5</sup> are methyl; and R<sup>4</sup> is methoxy or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II



wherein  $R^7$  is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum;

- (b) drying the granulate of step (a)
- (c) coating the dried granulate of step (b) with a first coating;
- (d) drying the first coated granulation of step (c);
- (e) coating the dried granulate of step (d) with an enteric coating.

166. The process for the preparation of a stabilized pharmaceutical unit dosage form according to claim 165 comprising the steps of:

- (a) granulating a mixture of 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellulose, polyvinylpyrrolidone, talc and magnesium stearate;
- (b) drying the granulate in step (a);
- (c) coating the dried granulate of step (b) with a first coating comprising hydroxypropylmethylcellulose, polyethylene glycol and a pigment;
- (d) drying the coated granulate from step (c); and
- (e) coating the dried granulate from step (d) with an enteric coating comprising a methacrylic acid ethyl acrylate copolymer.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/11389

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/44 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 00380 A (ASTRA) 7 January 1999 (1999-01-07)</p> <p>claims 1,11 — —/—</p>	<p>1-4, 9-11, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100,101</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

3 March 2000

Date of mailing of the international search report

10/03/2000

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11389

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 12817 A (WARNER-LAMBERT) 8 July 1993 (1993-07-08)  claims 1,2,5,7-9	1-4, 9-11, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100,101
X	EP 0 426 479 A (MCNEIL-PPC) 8 May 1991 (1991-05-08)  claims 1-4 column 6, line 13 column 6, line 36-38 column 7, line 1-16	1-4, 9-13, 15-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100-103
X	WO 98 22117 A (PROCTER & GAMBLE) 28 May 1998 (1998-05-28)  claims 1-3,5,8,11 page 4, line 31 -page 5, line 6	1-4, 9-13, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100-103

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No  
PCT/US 99/11389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9900380 A	07-01-1999	SE 510643 C AU 8135398 A SE 9702483 A	14-06-1999 19-01-1999 28-12-1998
WO 9312817 A	08-07-1993	AU 3247593 A	28-07-1993
EP 426479 A	08-05-1991	AT 101515 T AU 646230 B AU 6568990 A CA 2028746 A,C DE 69006684 D DE 69006684 T ES 2057439 T GR 90100786 A,B IE 64953 B IN 171746 A JP 3206052 A NZ 235877 A PT 95753 A US 5417980 A US 5204118 A ZA 9008775 A	15-03-1994 17-02-1994 09-05-1991 03-05-1991 24-03-1994 09-06-1994 16-10-1994 17-04-1992 20-09-1995 26-12-1992 09-09-1991 25-09-1992 30-09-1991 23-05-1995 20-04-1993 29-07-1992
WO 9822117 A	28-05-1998	EP 0941101 A NO 992469 A	15-09-1999 22-07-1999